



FORM: Application for Human Research

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TITLE: Effectiveness of Intense Therapeutic Ultrasound in the Management of Patients with Plantar Fasciitis

STUDY #: 2620384

DATE: April 5, 2014

IRB Approval #: 1404296558R002

Sponsor: **Guided Therapy**
33 S Sycamore
Mesa, Arizona 85202-1150 USA

Principal Investigator: **Dan Latt, MD, Ph.D.**
University of Arizona

**UACCESS EDOC NUMBER (FOR PROJECTS REQUIRING AN IRB
FEE)**

2620384

PROJECT TITLE: Effectiveness of intense therapeutic ultrasound in the management of patients with plantar fasciitis

INVESTIGATOR

Principal Investigator Name, Degree(s):	L. Daniel Latt, MD, PhD
Principal Investigator UA netID	dlatt
Status/Rank:	Assistant Professor
Center:	University of Arizona Medical Center
Section:	
Department:	Department of Orthopaedic Surgery
College:	Medicine
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ADVISOR CONTACT INFORMATION (REQUIRED FOR ALL STUDENTS AND RESIDENTS)

Name, Degree(s), UA NetID:	
Contact phone:	
Official University Email:	

ALTERNATE/COORDINATOR CONTACT INFORMATION

Name, UA NetID:	Cynthia Fastje, cfastje
Contact phone:	(520)626-7512
Official University Email:	cfastje@email.arizona.edu ; cfastje@ortho.arizona.edu

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SECTION 1: REQUIRED SIGNATURES**1. PRINCIPAL INVESTIGATOR**

I will conduct my research according to the University of Arizona HSPP Investigator Manual.

Signature	3/12/14	L. Daniel Latt, MD, PhD
	Date	Print Name

2. ADVISOR (FOR ALL STUDENTS AND RESIDENTS ACTING AS THE PI)

I will oversee the student researcher according to the University of Arizona HSPP Investigator Manual.

Signature	Date	Department
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3. SCIENTIFIC/SCHOLARLY REVIEW (CANNOT BE ASSOCIATED WITH THE PROJECT)

I have examined the proposal cited above, and find that the information contained therein is complete and that the scientific or scholarly validity of the project appears appropriate.

Signature	4/3/14	John Ruth, MD
jtr@email.arizona.edu	Date	Print Name
Official University Email	(520)626-4270	Phone number

4. DEPARTMENT/CENTER/SECTION REVIEW

I have reviewed this application and determined that all departmental requirements are met and that the investigator has adequate resources to conduct the Human Research.

Signature	4/3/14	John Ruth, MD
jtr@email.arizona.edu	Date	Print Name
Official University Email	(520)626-4270	Phone number

5. RESPONSIBLE PHYSICIAN (PROJECTS INVOLVING MEDICAL PROCEDURES WHICH THE PI IS NOT AUTHORIZED TO CONDUCT)

I am a physician licensed by the State of Arizona (or US license for the SAVAHCS). I will be responsible for ensuring that all procedures that are part of this project and that require the attendance of a licensed physician will have a suitable physician present during the procedures. If at any time this is not possible, I will inform the IRB before any procedures are conducted.

Signature	Date	Print Name
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6. NATIVE AMERICAN OR INTERNATIONAL INDIGENOUS POPULATIONS REVIEW

Signature needed only if research takes place in Indian Country or among international Indigenous populations, actively recruits Native Americans or international Indigenous populations for enrollment, and/or requires stratification of Native Americans or international Indigenous populations as one of the statistical analyses or study aims.

Social and Behavioral Projects: American Indian Studies, (520)621-7108
 Biomedical Procedures: Office of Outreach and Multicultural Affairs, (602)827-2327

I have examined the proposal cited above and advise that further appropriate tribal/Indigenous approval [] is [] is not necessary.

Signature

Date

Print Name

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SECTION 2: GENERAL INFORMATION

1. Not including this project submission, how many:
 - a. Human Research studies is the PI involved in as key personnel? 6
 - b. Active subjects are there in the PI's open Human Research study/ies? 21 (61 total)
 - c. Investigators are involved on the PI's open Human Research studies? 21
 - d. Research coordinators are involved on the PI's open Human Research studies? 1
2. What is the expected length of this project? 3 years
3. Retention of study materials before, during, and after completion of the project:
 - a. Where will the original signed consent and PHI Authorization documents be stored (building name and room)? Biomedical Research Labs (BRL) room B101
 - b. How long will the data/consents be kept after conclusion of the project? 6 years Other: _____
4. If the Human Research project is funded, identify all sponsoring entity/ies): Guided Therapy Systems
5. If funding support is from a federal agency (such as a training grant, infrastructure grant, salary support, project grant, etc.), list federal agency and grant number
6. Total funding amount **OR** per subject amount: _____
7. The Principal Investigator hereby affirms that ALL individuals who meet the definition of "investigator" for this project in the current "Policy on Investigator Conflict of Interest in Research" have completed the mandatory Conflict of Interest training (<http://www.orcr.arizona.edu/coi/training>) Yes
8. Will this project be registered on ClinicalTrials.gov because ...?
 - a. the local PI is the sponsor of the clinical trial (including NIH-funded clinical trials where the local PI is the funding recipient OR IND holder);
OR
 - b. The PI has been designated by a sponsor, contractor, grantee, or awardee to register the clinical trial to ClinicalTrials.gov, as the Responsible Party (responsible for conducting the trial, and has sufficient data rights)
If yes, please check the appropriate box:
 ClinicalTrials.gov "NCT" number for this trial (define):
 Registration pending

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Clinical trial does not require registration (click above to see what studies qualify)

SECTION 3. PROJECT NARRATIVE**1) Background**

The primary objective of this study is to evaluate the efficacy of combining intense therapeutic ultrasound (ITU) with standard care for the treatment of chronic plantar fasciitis. A secondary objective is to evaluate the tolerability and safety of intense therapeutic ultrasound in the treatment of plantar fasciitis.

These objectives will be accomplished through the following specific aims:

Aim # 1: Compare patient reported outcomes of pain, function and level of activity for subjects treated with standard of care plus ITU (ITU group) to those treated with standard of care plus sham ITU (control group).

Aim # 2: Compare the changes in plantar fascia thickness in subjects treated with standard of care plus ITU to those treated with standard of care plus sham ITU.

Aim # 3: Evaluate the tolerability and safety of ITU for the treatment of chronic plantar fasciitis Chronic Plantar Fasciitis. Chronic plantar fasciitis (CPF) is a common cause of plantar heel pain that is a result of a degenerative process of the plantar fascia and its surrounding perifascial structures. It is the most common cause of heel pain, affecting 10% of the U.S. population, and one of the most common foot and ankle problems. One study showed that individuals with this disease scored significantly lower in general health-related quality of life in addition to foot specific quality of life (pain and function).

The plantar fascia, or plantar aponeurosis, originates on the posterior tuberosity of the calcaneus and inserts into the proximal phalanges of the toes. It acts like a cable, which tightens with flexion of the metatarsophalangeal joints, the “windlass” mechanism, thereby restoring the arch during mid-stance, stiffening the medial column of foot for push-off and transferring the force of the gastrocnemius muscle contracture to the ground. Although the exact etiology of CPF is unclear, the predominance of evidence indicates that it is the combination of age and overuse which lead to degenerative changes within the fascia that result in the symptoms associated with this disease. The most common presentation for patients with plantar fasciitis include pain with the first few steps in the morning, pain at the beginning of the activity that resolves with continued activity, pain and stiffness with prolonged standing, and pain at the end of the day.

The diagnosis of CPF is made clinically based on history and physical exam. Confirmation with diagnostic imaging may be necessary when the symptoms are atypical or are refractory to treatment. MRI is a useful diagnostic tool to evaluate for plantar fascia thickening and edema in and around the fascia, both of which are consistent with the diagnosis of CPF. In addition, many physicians use MRI to exclude other causes of plantar heel pain. Ultrasound can also be used to measure the thickness of the plantar fascia. Multiple studies have shown that patients with CPF have increased thickness of the fascia compared to asymptomatic individuals. Mean thickness in these studies for subjects with CPF range from 4.8-6.5 mm as opposed to 2.3-4.0 mm for subjects without the disease. One of the studies showed that the thickness was increased in medial, central and lateral bands of plantar

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fascia uniformly along with 68% of patients with CPF reporting central band tenderness as opposed to 26% having lateral band tenderness. In addition to the evidence of inflammation, the presence of a hyper-echoic lesion in the plantar fascia was noted in 68% to 84% of patients with CPF. Diagnostic ultrasound has also been used to quantify the effectiveness of treatments such as extra-corporeal shock wave therapy, NSAIDs and Botox injections for subjects with CPF.

More than twenty different treatments have been used for plantar fasciitis. The combination of rest, ice, stretching and NSAIDs are used as initial management in most patients and have been shown to effectively treat symptoms in 90% of patients in less than 12 months. However, 10% of patients fail conservative management and continue to have symptoms beyond 12 months (termed refractory plantar fasciitis or RPF). Surgery consisting of partial plantar fascia release or gastrocnemius recession is often considered in these patients. However, the outcomes of surgery are not uniformly positive with 50% of patients reporting residual symptoms. Moreover, evidence supporting surgical treatment of RPF is weak as there are no randomized controlled trials comparing its efficacy to other treatments. Thus, for many patients the risks of surgery such as arch instability, prolonged wound healing, and longer rehabilitation times simply outweigh the benefits. Is there a non-invasive treatment that can be used as an adjunct to speed healing in patients with CPF and as an alternative to surgery in those with RPF? The primary objective of this study is to evaluate the efficacy of combining the non-invasive treatment with intense therapeutic ultrasound (ITU) with standard care for the treatment of chronic plantar fasciitis. A secondary objective is to evaluate the tolerability and safety of intense therapeutic ultrasound in the treatment of plantar fasciitis.

Intense therapeutic ultrasound (ITU). Various types of ultrasound have been used to treat soft tissue injuries since the 1930s. Intense therapeutic ultrasound (ITU) is a recently developed ultrasound based therapy in which sound waves are concentrated to produce selective thermal coagulative change over a small area while leaving the remaining regions unaffected. ITU has been used clinically for treating the facial skin for the past decade and it has recently received FDA approvals for non-surgical brow and submental tissue lifting. Over 300,000 patients worldwide have been treated using this technology. Clinical studies have shown that 85% of subjects receiving this treatment on facial skin tissue showed an improvement in facial lifting with no significant pain, erythema, inflammation or scarring. Histologically, it has been shown that ITU induces the production of dermal collagen with thickening of the dermis and straightening of the elastic fibers in the reticular dermis. On-going research in our laboratory has shown that ITU can improve healing of damaged Achilles tendon in a rabbit model. Preliminary results showed an increase in markers for wound healing (e.g. VEGFa, TNF α , IL-1 β , and TGF β 1) and a decrease in markers for scar tissue formation (e.g. COL1 α 1, COL1 α 2, and COL2 α 2) in injured rabbit tendon treated with ITU compared to injured, untreated rabbit tendon. These results have led us to want to explore the possibility using ITU to treat patients with CPF.

2) Lay Summary (approximately 400 words)

The purpose of this study is to assess the effectiveness of ITU in the treatment of CPF by comparing pain, function, and change in plantar fascia thickness in subjects treated with ITU in addition to standard of care to subjects that are treated with standard of care alone. The primary outcome measure will be a computer adaptive questionnaire where pain, function and level of activity will be compared between the two groups. In addition, with the use of diagnostic ultrasound, plantar fascia thickness and presence or absence of hyper-echoic lesion will be compared between the two groups. Finally, the safety and tolerability of ITU will be monitored through the course of the study. It is hypothesized that patients receiving ITU in addition to standard of care will have a more rapid resolution of their pain, faster return to activities, and a greater decrease in plantar fascia thickening on ultrasound as compared to those only receiving standard of care.

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3) Setting of the Human Research

The PI is an assistant professor in the Department of Orthopaedic Surgery and surgeon with the University of Arizona Health Network. Subjects will be recruited from the outpatient clinic of Drs. Daniel Latt (PI) and Peg Chilvers. The age, gender, height, weight, activity level, pain level, and physical exam findings of patients will be obtained directly from the subject, the subject's medical record, or from direct examination and then recorded in a password protected excel file. The online survey can be completed from any computer available to the subject. Intense therapeutic ultrasound and diagnostic ultrasound will be administered in the Human Movements Biomechanics Lab (BRL B101).

4) Resources available to conduct the Human Research

Equipment for intense therapeutic ultrasound will be provided by Michael Slayton and Rich Amodei from Guided Therapy Systems. The equipment for measuring height and weight will be in the orthopedic clinic. Personnel available to conduct the study include 2 surgeons, 1 clinical research coordinator, 2 sonographers, 1 medical student, and 2 undergraduate assistants. These individuals will be available to recruit and consent patients, coordinate and conduct the study, analyze the data, and produce a manuscript.

5) Study Population

Male and female adults (18 years or older) with plantar heel pain and point tenderness near the medial calcaneal insertion of the plantar fascia for at least three months without improvement will be considered for inclusion into the study. Subjects with diabetes, bilateral plantar heel pain, current systemic or local infection, previous foot surgeries, other foot/ankle pathologies (inflammatory arthritis, gout, neurologic disorders, connective tissue disorders and malignancy), contraindications to the use of NSAIDs, and pregnancy will be excluded. The target enrollment of this pilot study is 50 participants.

6) Recruitment Methods and Consenting Process

Subjects will be recruited utilizing public media, list serves, community organizations, and via referral. Please see the attachments to this application for an electronic media and brochure representations of the advertisements to be utilized. We would like to select from the following wording to produce recruitment materials -

"We are seeking adults with chronic heel pain. Have you had chronic heel pain? Chronic heel pain is pain which has been present for at least 3 months and may be the result of plantar fasciitis. Have you had heel pain for the last 3 months? It may be the result of plantar fasciitis. Plantar Fasciitis is a painful, inflammatory condition occurring where the plantar fascia attaches to the calcaneus (heel bone). The most common symptoms are 1) pain with the first few steps in the morning, 2) pain at the beginning of an activity which improves as the plantar fascia is stretched during the activity, 3) pain and stiffness with prolonged standing, and 4) pain at the end of the day. The standard treatment of Chronic Plantar Fasciitis consists of stretching, anti-inflammatory medications (NSAIDS), and heel cups. Despite these treatments, 5% - 20% of patients will still have symptoms at 1 year! Participate in a study to determine the effectiveness of Intense Therapeutic Ultrasound for the treatment of Chronic Plantar Fasciitis. What is Intense Therapeutic Ultrasound? Intense Therapeutic Ultrasound (ITU) is a noninvasive method of healing tissues with sound waves. ITU promotes collagen generation and is FDA approved for the non-surgical lifting of the brow. What is the purpose of this study? The purpose of this study is to determine if intense ultrasound can promote healing of plantar fasciitis. This study will determine the effectiveness of ITU in speeding the healing of plantar fasciitis. The time required

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to heal will be compared for traditional treatment methods + placebo to that required by traditional treatment + ITU. Every subject will receive anti-inflammatory medication, a viscoelastic heel cup, and physical therapy. Patients receiving just these treatments will be compared to those also receiving ITU treatments. Who can participate? The following criteria are required for participation: A physician associated with the study has diagnosed you with plantar fasciitis. To be eligible you need to have chronic heel pain that is diagnosed as plantar fasciitis by a physician associated with the study. The/your symptoms exist in only one foot. You must not have diabetes or be pregnant. You must be 18 years or older. What will participation require? You will need to be assigned to either a control group (standard medical care) or to an experimental group (standard medical care + ITU). You will need to not use any other treatments. You will need to commit to the assigned treatment for 3 months. You will need to answer an additional online or telephone questionnaire at 6 months. Why should I participate? Although you will not receive payment, what is learned may benefit others! To participate, please call [contact information]. If interested, please call [contact information] or send an email to [contact information] and provide preferred contact information."

In addition to anatomical labeling of the *achilles tendon, calcaneus, and plantar fascia*, we would like to use the captions, "*Inflammation of the plantar fascia can cause heel pain*" and "*stretching the plantar fascia*."

Interested individuals who contact the laboratory will have the logistics of the study explained and be referred to the clinic for diagnosis and treatment of heel pain. All patients diagnosed with plantar fasciitis by participating physicians will be contacted by the research team to discuss the details associated with participation. We would like to obtain a temporary deferment of authorization to obtain contact information from the electronic medical record for those individuals who are initially identified in the clinics by participating physicians. Additionally, we would like permission to provide the consent and authorization forms and other information by e/mail should this be conducive to obtaining informed consent. The mailing is for informational purposes only to allow the subject more time to consider participation in the study. The informed consent process will be completed in person. Both English and Spanish versions of the consent forms will be utilized, although the Spanish consent form will be submitted as a modification once the English version is approved. Finally, we would like to provide a map and information sheet to assist participation in the study (see attachments).

7) Procedures involved in the Human Research

After obtaining informed consent and authorization from the subject, study personnel will verify the screening of participants utilizing the inclusion/exclusion criteria and collect the following information- age, gender, height, weight, activity level, pain level, and physical exam findings including x-rays - which will be recorded on the data abstraction sheet (see attachment). The activities strictly associated with the research are the assignment to a study group (Control or ITU), the administration of patient reported outcome measures (questionnaires), and therapeutic and/or diagnostic ultrasound (Table 1). Additionally, adverse events will be recorded at each visit (see attachment). Treatment tolerability will be prior to, immediately after, and at 2 days post-treatment.

Standard of care is integrated into both arms of the investigation and includes a structured physical examination, the use of an NSAIDs for 3 weeks (Naprosyn 500 mg po bid or Ibuprofen 800 mg po tid taken with meals), viscoelastic heel cups for 12 weeks, and supervised physical therapy with home exercise program for 6 weeks. These components are described below-

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Table 1. Calendar of Activities

Timeline	Standard of Care	Research Activity
-1	focused history, x-rays, NSAIDs, heel cups	Informed consent and assessment of inclusion/exclusion criteria; enrollment in the study (randomization to treatment group)
0	NSAIDs, heel cups, focused exam	questionnaires; ultrasound (diagnostic & treatment)
2 weeks	NSAIDs, heel cups, focused exam	questionnaires; ultrasound (diagnostic & treatment)
4 weeks	heel cups, focused exam	questionnaires ultrasound (diagnostic)
6 weeks	heel cups, focused exam	questionnaires ultrasound (diagnostic)
12 weeks	heel cups, focused exam	questionnaires ultrasound (diagnostic)
24 weeks		questionnaires

Structured physical examination. The focused exam will consist of assessment of hindfoot and midfoot alignment, inspection for swelling, palpation of the calcaneus and entire plantar fascia, range of motion of the ankle with the knee flexed and with the knee extended, and calcaneal squeeze test. Pertinent positive findings on exam include: valgus hindfoot, midfoot planus, tenderness to palpation at the insertion of the plantar fascia onto the calcaneus, ankle dorsiflexion less than 10 degrees with the knee extended or greater than 10 degree augmentation in ankle dorsiflexion with the knee flexed. Pertinent negative findings include: lack of swelling at the ankle and midfoot, no tenderness at the Achilles insertion, the retrocalcaneal bursae, along the arch, posterior to the medial malleolus, or at Baxters point, and positive calcaneal squeeze test.

Physical Therapy. Supervised physical therapy will occur two times per week and include gastrocnemius stretching, plantar fascia specific stretching, modalities (ice and heat), and plantar fascia deep tissue massage (see instructions to PT appendix 2 of the protocol). Use of advanced modalities such as iontophoresis, phonophoresis, or TENS will not be permitted. The home exercise program will consist of PF specific stretch and gastrocnemius stretch to be done for ten minutes two times per day (see home exercise program handout, Appendix 2 of the protocol). Subjects will be required to record the frequency of each exercise in a logbook (see Appendix 3 of the protocol).

The research components are described below-

Randomization and Blinding. Suitable subjects will be randomly assigned (1:1) to receive standard of care with a sham ultrasound treatment (Control group) or standard of care + ITU treatment (ITU group) by the application of an algorithm (e.g. even vs odd) to the number provided by a random-number generator. Most members of the research team and the subject will be blinded to group assignment. Only the clinical research coordinator and ultrasound treatment team will be privy to the subject's group assignment.

Patient Reported Outcome Measures (Aim 1). The principal aim of this study is to compare the efficacy of treatment and time course of response to treatment between the two groups using validated

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patient reported outcome measures assessing pain, function and level of activity. Subjects will complete validated patient reported outcome questionnaires assessing pain, function and level of activity prior to initiating treatment and at 0, 2, 4, 6, 12, and 24 weeks after starting treatment.

Pain will be assessed using the of the foot function index pain subscale (FFI-P) and the subject reported outcome measures (SROM). These two instruments have been used to assess pain in previous studies of plantar fascia treatments. (Please see Appendices 1-D and 1-E of the Protocol.)

Function will be assessed using two validated PRO instruments the PROMIS PF CAT and the FAAM. The PROMIS PFCAT is a subject relevant outcome measure that uses computer adaptive survey questions to assess the patient's pain and function in relation to daily activities. (Please see Appendix 1-A of the Protocol.) The FAAM has been shown to be a reliable, responsive, and valid measure of physical function for individuals with a broad range of musculoskeletal disorders of the lower leg, foot, and ankle. (Please see Appendix 1-B of the Protocol.)

Level of Activity will be assessed using the activity subscale of FAAM. This subscale scores quantitatively the level of difficulty subjects often face when they perform basic activities of daily living. It has shown to be an accurate and reliable predictor of the activity level while performing day-to-day activities. (Please see Appendix 1-B of the Protocol.)

Diagnostic Ultrasound (Aim 2). Diagnostic ultrasound will be utilized to compare the changes in plantar fascia thickness that occurs over time in subjects treated with standard care to those treated with ITU plus standard of care. Diagnostic ultrasound imaging will be performed with an FDA approved ultrasound scanner (Spark® System, Ardent Sound, Inc. – Mesa, AZ, see Appendix 6 of proposal) using a coupling gel (Polysonic®, Parker Laboratories, Inc., Fairfield, NJ, see Appendix 7 of the attached proposal) by a trained sonographer or physician. The subject will be positioned prone on an exam table with the feet over the edge of the table. The plantar fascia of the affected and contralateral feet will be imaged. The width and depth of the fascia as well as the size and location of a hyperechoic lesion, when present, will be recorded using both long and short axis imaging. Change in plantar fascia thickness relative to the baseline measurement will be calculated. Decreased thickness of 0.8 mm or greater will be considered clinically significant as these changes have been shown to correlate with decreased pain and increased mobility.

Experimental Treatment: Intense Therapeutic Ultrasound (ITU). Subjects in the ITU group will receive standard treatment plus two treatments (at week 0 and week 2) of ITU to the affected plantar fascia (Table 1 in red). ITU treatment will be performed using a GEN II system (Guided Therapy Systems, Mesa, AZ). (Please see Appendix 5 of the Protocol.) We are seeking classification as a non-significant risk (NSR) device. (Please see the attached NSR statement.) Trained study personnel will conduct the treatments. The treatment session will last 15 – 20 minutes. During this time the subjects will be required to lay prone position on an exam table with their feet hanging over the end of the table. An average energy up to 5 joules / thermal zone will be administered to the symptomatic Plantar Fascia in a linear pattern along the Plantar Fascia (Figure 1) with up to 50 lines. Each line will include individual thermal zones, less than 1 mm³ in volume, centered at 10 – 13 mm depth, and approximately 2 mm apart.

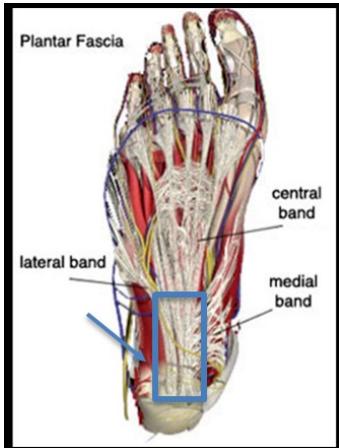


Figure 1: The treatment site located around the insertion of the plantar fascia onto the posterior process of the calcaneus

Assessment of Safety and Tolerability (Aim 3). Subject self-assessments of treatment tolerability will be conducted immediately after, two days after (phone survey) and two weeks after treatment using a 10-point visual analog scale (VAS, see Appendix 1-C). The subject will be asked to report their current level of pain and the maximum level of pain experienced over the last two days. The VAS is the standard for assessing pain for both clinical and research purposes. Recording of adverse events will take place at all visits (see adverse event reporting form Appendix 4 in the protocol). Adverse events and serious adverse events will be monitored throughout the study. A treatment will not be administered if there is residual pain/discomfort experienced by the subject from the previous treatment.

Statistical analysis. Data will be assessed for variance homogeneity and normality. FFI-P, PFCAT, and FAAM scores before and after intervention will be compared between the two groups using a paired t-test. Additionally, the mean thickness of the plantar fascia will be compared between the two groups before and after treatment and significance determined utilizing paired t tests. P<0.05 is considered to be statistically significant.

8) Risks to subjects

Exposure to ITU may produce short-term sensations which may cause discomfort and mild erythema for up to a few hours following the exposure. No detrimental side effects have been reported in previous clinical trials investigating similar devices in which ultrasound energy was applied to the neck and face. Additionally, the ITU in this investigation will utilize lower power parameters than those reported for these similar devices. We are seeking classification of the GEN II system (Guided

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Therapy Systems, Mesa, AZ) as a non-significant risk device. (Please see the attached NSR statement.) Adverse events will be recorded at each visit (see appendix 4 of the protocol).

Additionally, x-rays will be obtained as part of the standard care. A small risk exists of developing cancer later in life as a result of exposure to radiation.

Finally, risk of exposure of protected health information (PHI) exists. However, we have minimized this risk by implementing three levels of precaution. Access to protected health information will be restricted to the minimum number of individuals required to complete the tasks. The files containing the PHI will be kept electronically and geographically separate from the data files with entries identified only by a randomly generated number to be used as the PHI key. Both files will be encrypted and password protected and then stored on password protected, secured computers.

9) Potential benefits to subjects and/or society

Subjects receiving intensive therapeutic ultrasound treatment may experience faster healing time, decreased pain and return to full function earlier as a result of the treatment. Patients not placed into the ITU group will receive no additional individual benefit by participating in the study. The results of this study may lead to further research or widespread clinical application of ITU in turn increasing knowledge in this area or improving the care available to individuals affected by plantar fasciitis. However, in general the subjects will obtain no significant benefit by participating in the study.

10) Provisions to protect the privacy of subjects and the confidentiality of data

The consenting process will be initiated in the clinic with the physicians in the privacy of an exam room. The names and contact information for potential subjects will be kept in a password encrypted excel file on a password protected, secured computer. Only the minimum number of research personnel required to complete the consenting process will have access to PHI. Once enrolled in the study a unique patient identifier will be used in subsequent date files generated in the study. . A list linking subjects to identifiable information will be stored on a password protected, secured computer. This list will only be accessible to the study coordinator during the study and to the PI (L Daniel Latt, MD PhD) following data analysis. Should the arrival of subjects in the lab overlap, we will have a separate room available apart from the lab so that the consenting and subsequent exam and treatment can be conducted in privacy. Should a participant decide to leave the study, the patient's PHI records will be destroyed, but the data will be retained. Upon closure of the IRB project, all patient identifiers will be destroyed.

11) Access to Private Information**a. Authorization for access to Protected Health Information (PHI)**

We are requesting a temporary waiver of authorization so that we may obtain contact information from the medical records for those subjects identified in clinic as interested in the study. We will obtain authorization for PHI during the consenting process. This request is based upon the following justification-

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- 1) The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on , at least, the presence of the following elements;
 - a) An adequate plan to protect the name and phone number from improper use and disclosure has been implemented through the utilization of password protected files. Additionally, the PHI will be obtained and accessed only by the minimal number of investigators required to conduct the study. Furthermore, the computer containing the PHI will be password protected and secured.
 - b) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law, has been implemented in that the contact information will be destroyed if the subject declines participation. An authorization will be obtained prior to the additional collection of PHI.
 - c) Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by HIPAA, are hereby provided in that the PHI will only be utilized to conduct the study as described within the attached protocol.
- 2) The research could not practicably be conducted without the waiver or alteration of the HIPAA authorization requirement because access to contact information is required to begin the process of informed consent. If the subject indicates that they are not interested in participating, their contact information will be removed from the encrypted data file. No other information will be obtained from the records until authorization is provided by the subject.
- 3) The research could not practicably be conducted without access to and use of the protected health information because obtaining authorization at the clinic for participation in the study may not be consistently feasible.

12) Cost to subjects

The proposed research has no associated costs to the subjects.

13) Subject compensation

The subjects will not be compensated.

14) Medical care and compensation for injury

If an injury occurs, medical care is available. No funds are available to cover compensation for any injury incurred as a result of participation in this investigation.

15) Withdrawal of subjects

Subjects may withdraw from the study at any time either in person, in writing, or by telephone. Subjects withdraw by contacting either Dr. Daniel Latt or the project lead. Abrupt withdrawal

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presents no risk. Should subjects fail to comply with instructions given to them, they may be withdrawn from the study.

16) Sharing of results with subjects

The results of the study will not be shared with subjects.

17) Information management

N/A

18) Drugs, Devices, and Gases

Equipment for intense therapeutic ultrasound will be provided by Michael Slayton and Rich Amodei from Guided Therapy Systems and operated by trained sonographers.

- a) Name of drug/device: GEN II
- b) FDA approval status of the drug/device: We are seeking classification as a Non-Significant Risk (NSR) Device with the following reasons-
 - (a) GEN II will not be utilized nor is intended to be utilized as an implant. Additionally, the device does not present a potential for serious risk to the health, safety, or welfare of a subject.
 - (b) GEN II is not purported or represented to be for a use in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject.
 - (c) The GEN II device is not of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject.
 - (d) The GEN II does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.
- c) The GEN II will be controlled by the PI and/or representatives of the sponsor, Guided Therapy Systems:
 - i) The device will be stored in the PI's laboratory located in the Department of Orthopaedic Surgery, Biological Research Buildings, Building B Room 101 or in possession of GTS representatives.
 - ii) The site is sufficiently secure to protect the equipment.
 - iii) The storage condition for the equipment is not of concern beyond normal sheltered conditions.
 - iv) The GEN II device does not require stringent control and tracking of utilization.

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- v) Trained sonographers will perform the ITU utilizing the GENII system.
- vi) Disposal issues are not relevant to the use of the GEN II system.

SECTION 4: LIST OF ATTACHMENTS FOR THIS SUBMISSION

Document Name	Version Date
1. F107 v030614	1. 3/6/14
2. Latt CV_Nov 2013	2. 11/2013
3. Ortho - Planters Fasciitis Broch_v7	3. 2/2014
4. Craig's List	4. 3/4/14
5. T502a - ICF Consent Form v031014	5. 3/10/14
6. T504a - PHI Authorization Form v031014	6. 3/10/14
7. T504b- PHI Autorizacion Spanish v031414	7. 3/14/14
8. map	8. 9/23/13
9. ITU protocol latt final	9. 4/5/14
10. AE Log	10. 4/5/14
11. NSR Statement 022614	11. 2/26/14
12. ITU-PF patient Instructions	12. 3/10/14

Submission List for F200: Application for Human Research**Required items for all F200 submissions:**

- F107: Verification of Training Form
- Current PI/Co-PI CVs or biosketch, if not included with copy of grant application

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Other Items as applicable:

- **Biosafety Review letter** (for UA - Institutional Biosafety Committee)
- **Certificate of Confidentiality**
- **Compressed Gases Review letter** (for UA – Research Instrumentation)
- **Contract** – complete or draft copy of contract including budget
- **Data Collection Tools** – surveys, questionnaires, diaries not included in the protocol, data abstraction form for records review
- **Data Monitoring Charter and Plan**
- **Drug/Device information** – Investigator's Brochure, drug product sheet, device manual, user's manual, instructions for use, package insert, IND/IDE documentation, FDA 1572 form, 510k indication, FDA exemption, sponsor determination of device risk, etc.
- **Export Control Review**
- **Grant Application(s)** – complete copy of grant, regardless of home institution or funding agency, and a copy of the Notice of Grant Award
- **Informed Consent/Permission/Assent Form(s)** – including study specific release of information documents, DHHS approved sample consent forms. If consent will not be documented in writing, a script of information to be provided orally to subjects
- Other Approval letters (e.g., school districts, Tribal, other IRB approvals)
- **Participant Materials** – All written materials to be provided to or meant to be seen or heard by subjects (e.g. study newsletter, physician to participant letter, wallet cards, incentive items, holiday/birthday cards, certificates, instructional videos/written guides, calendars, certification of achievement, etc.)
- **PHI Authorization Form(s)**
- **Protocol** – including all amendments/revisions, sub- or extension-studies
- **Radiation Safety Review letter**
- **Recruitment Materials** – telephone scripts, flyers, brochures, websites, email texts, radio/television spots, newspaper advertisements, press releases, etc.
- **Scientific Review Committee** letter (for cancer related projects – AZCC SRC; other units as applicable if the unit has a scientific review committee)
- **Site Authorizations** for research purposes and/or access to administrative records/samples
 - External sites (such as schools, other hospitals or campuses, etc.)
 - UAHN University Campus, South Campus and clinics Site Review Authority (SRA) approval
- **Supplemental site information** (for sites engaged in research where the UA is the IRB of record)
 - Copy of any approvals granted from that site (including determinations if this site has an IRB of its own)
 - Site-specific F107
 - Copy of the site's human subjects training policy
 - CV and medical license (if applicable) of site PI
- **Travel Authorization documentation** (for UA – Office of Global Initiatives)
- **Use of retrospective research samples and/or data** – IRB approval letter, original consent under which samples/data were collected, letter allowing access to samples

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Submitting documents to the IRB

All materials must be typed and submitted electronically. Maintain electronic copies of all information submitted to the HSPP office in case revisions are required. It is recommended that version dates be used while naming documents.

1. Documents must be submitted to the VPR-IRB@email.arizona.edu account and not to individual staff email accounts. After contact by a staff member future correspondence may be communicated directly to the staff member concerning the submission.
2. **If acknowledgement of receipt is needed, please request a "Read Receipt" through your email server.** If you use Microsoft Outlook 2007, this is accomplished by clicking "Options" and choosing the "Request a Read Receipt" checkbox in a new email.
3. One submission request per email (e.g. one new project submission, one continuing review plus attachments, or one modification request).
4. All submissions must have signatures. An email acknowledgement in place of a signature will not be acceptable. If electronic signatures are not available for use, the signature pages may be signed and scanned as a separate Adobe PDF document and attached to the submission email.
5. **Microsoft Word documents are REQUIRED** for (applications, consents, recruitment materials, and data collection instruments (if available). PDFs may be submitted for documents that typically are not revised by the IRB (e.g. Investigator Brochures, sponsor protocols).
6. The email subject line must include: IRB # (if assigned one), PI Last Name, and type of submission (Modification, New Project, Continuing Review, Reportable Item, etc.).
7. The email must provide a list of the documents submitted for review. While the documents attached do not have to adhere to a specific naming scheme, it is requested that each document be named to clearly reflect what is inside.

Submissions not following these guidelines will be returned without review